Mayo Clinic Cancer Center

MC16C1: Double-Blinded, Placebo-Controlled Pilot Trial to Explore Whether Lipids Prevent Carboplatin and Oxaliplatin Hypersensitivity Reactions

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Protocol Resources

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*No waivers of eligibility per NCI

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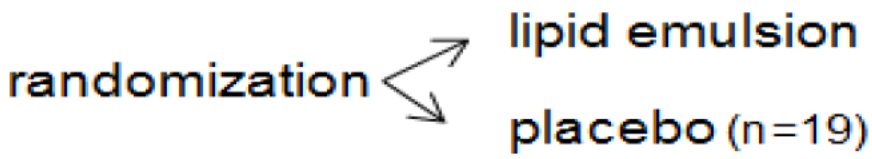
Schema



This 40-patient pilot, double-blinded, placebo-controlled trial entails the administration of lipids versus placebo x 1 dose before **every** dose of carboplatin or oxaliplatin. The primary endpoint will be time-to-carboplatin or oxaliplatin hypersensitivity reaction, and exploratory laboratory endpoints will be examined during the first cycle of carboplatin or oxaliplatin.

Unacceptable adverse Events → **Off Study**
Patient refusal

Max cycle length = 28 days (will vary by agent please see Section 7.0 for details)
Max study duration per patient = 2 years after registration

Generic name: lipid emulsion Brand name: Intralipid® 20% Mayo Abbreviation: NA Availability: Provided for study	Generic name: placebo Mayo Abbreviation: NA Availability: Provided for study

1.0 Background

1.1 The Important Role of Carboplatin and Oxaliplatin in Cancer Treatment

Carboplatin is a key antineoplastic agent for the treatment of ovarian cancer. Over the past decade, it has served as the backbone chemotherapy agent for the majority of postoperative ovarian cancer trials. Indeed, the well-established term "platinum sensitive disease" refers to the 6-month cancer-free interval after which it becomes acceptable to re-expose patients to this drug upon cancer recurrence, thus further underscoring the pivotal role of carboplatin for the treatment of this malignancy [1-5]. Carboplatin has also become a key drug in the treatment of other gynecological malignancies, such as endometrial cancer.

The same can be said for oxaliplatin, which is used extensively in the treatment of patients with gastrointestinal cancers. One might argue there are few/no gastrointestinal cancers that cannot be treated with an oxaliplatin-based regimen. Oxaliplatin is a key drug as adjuvant chemotherapy in colorectal cancer patients [see extra references].

1.2 Carboplatin and Oxaliplatin Hypersensitivity Reactions: Incidence, Risk Factors, and Management

Carboplatin and oxaliplatin hypersensitivity reactions can interfere with cancer treatment and compromise such ongoing cancer therapy. These reactions are **life-threatening and obvious** when they occur. They are characterized by itching, coryzal symptoms, nausea and vomiting, dyspnea, wheezing, hypotension, confusion, and, at times, even death. For carboplatin, reactions occur in only 10% of patients during the first 6 cycles of chemo-therapy, but their incidence jumps to approximately 30% shortly after the 7th cycle of carboplatin [6]. For oxaliplatin, the incidence of appears to increase with the 7^{th} cycle of treatment as well to a rate of approximately 20% with a steady increase in incidence thereafter [see extra references].

Risk factors for these reactions include a predisposition to allergies, a higher cumulative dose of the culpable drug, and specific choice of concurrently administered chemotherapy agent [6-14]. One of the most powerful risk factors is time-dependent: patients with a 13 month or longer carboplatin-free interval have a **22-fold increased risk** of a reaction upon re-exposure [8]. Although earlier studies had invoked skin testing to identify patients at risk, most medical centers do not make use of this approach because of suboptimal predictive sensitivity and specificity, mutilating cutaneous effects, and undue chemotherapy exposure for healthcare workers and the environment [15]. Vigilance during drug infusion and either desensitization or abandonment of either carboplatin or oxaliplatin post-reaction comprise the current approach to platinum drug administration.

Desensitization enables carboplatin or oxaliplatin to be dispensed once again with small, incremental doses administered in a monitored setting until the entire intended dose is infused [16-21]. Desensitization has drawbacks: **1)** a several-hour commitment with **every** infusion; **2)** reduced but **ongoing** risks of hypersensitivity signs/symptoms with mounting risk over time; and **3)** exorbitant cost. At our institution, over one year, we observed cumulative, multi-cycle patient costs with desensitization to carboplatin specifically of **$1 million – over a 10-fold increase** over that incurred from routine outpatient carboplatin administration. An inexpensive prophylactic intervention that **eliminates carboplatin and oxaliplatin reactions** would be advantageous for many reasons.

1.3 Addressing a Gap

Few studies have examined **a prophylactic approach** to these reactions. A commonly-used intervention to prevent reactions, as proposed here, provides a safe, potentially cost-effective, and novel way of managing the risk for a carboplatin hypersensitivity reaction.

Table 1: RANDOMIZED TRIALS WITH DOXIL® + CARBOPLATIN *VERSUS* CARBOPLATIN WITH **NO** DOXIL®

TRIAL	N	REACTION RATE with DOXIL® (%)	REACTION RATE with CARBOPLATIN with **NO** Doxil® (%)
Markman, 2010 [22]*	61	0	30
Bafaloukos, 2010 [23]*	189	8	30
Pujade-Lauraine, 2010 [24]	976	15	33

*Not specified whether Doxil® was infused first.

1.4 Hypothesis: Lipids Prevent Carboplatin Hypersensitivity Reactions

This proposal focuses on **a seminal, recurrent observation:** relapsed cancer patients who receive liposomal doxorubicin (Doxil®) with carboplatin **suffer fewer carboplatin reactions** (**Table 1**)**.** Of note, in Table 1, some of the reactions with Doxil® might perhaps have been attributable to Doxil,® which at times can also cause hypersensitivity reactions – and perhaps **not at all to carboplatin**. Nonetheless, throughout the published literature, the rate of carboplatin hypersensitivity reactions is consistently <30% with the incorporation of Doxil®, even in single-arm trials [22-30]. The seminal observation that Doxil®, a liposomal form of doxorubicin, is associated with lower rates of carboplatin hypersensitivity reactions gives rise to the following novel **HYPOTHESIS: the infusion of a lipid emulsion (the same used for nutrition support) – in effect, liposomal doxorubicin but without the doxorubicin – prevents carboplatin hypersensitivity reactions.**

Three points underscore the plausibility of this hypothesis. First, again, Doxil® is associated with fewer carboplatin hypersensitivity reactions [22-30]. Lipid emulsions, as commonly prescribed for parenteral nutrition, simulate Doxil® infusions by providing a near identical therapeutic platform -- same volume, similar lipids – but with **no** Doxil®. Second, carboplatin hypersensitivity reactions are most commonly type I hypersensitivity reactions (and less commonly type IV hypersensitivity), as indicated by a series of studies that demonstrate IgE mediation [10,11,31,32]. Lipid emulsions, particularly those that are heavily soy-based and commonly prescribed today, have immunosuppressive effects [33-35]. They transiently suppress T-cell function, modulate B cell populations, and confer other suppressive effects on inflammation [33-35]. Of special relevance, preclinically, Arnaez and others, showed that, although carboplatin induces histamine release from mast cells, it does so by **unique mechanisms – speculatively, via complement activation or direct mast cell degranulation -- but nonetheless unrelated to conventional approaches** [36]. These findings are in keeping with what occurs clinically where carboplatin reactions remain problematic and suggest that a **broad-based immunomodulator, such as a lipid emulsion,** merits testing, as proposed here.

Third, and very importantly, multiple reports indicate that **lipid emulsions (the same used for nutrition support) are critically life-saving in patients with severe drug-induced adverse events** [37-47]. These reports describe the resuscitative role of lipids -- often as a heroic last resort -- in patients with overdoses from mepivacaine, bupivacaine, olanzapine, doxepin, flecainide, venlafaxine, moxidectin, atenolol, nebivolol,

lamotrigine, propranolol, verapamil, diltiazem, atenolol, amitriptyline, glyphosate herbicide, and others [37-47]. In effect, lipids serve as a rescue for patients suffering from toxicity from a lipophilic drug**:** in some reports, patients who were suffering ventricular tachycardia and who were seizing recovered promptly upon receipt of a lipid infusion. It appears that the infused lipids bind to the lipophilic drug and displace it from the target organ. In the case of **carboplatin and oxaliplatin – both of which are highly lipophilic – lipids presumably bind to it, displace it from basophils and mast cells, and thereby prevent the hypersensitivity reaction**.

Lipid emulsions are used as part of parenteral nutrition to increase the caloric content of nutrition support and to prevent essential fatty acid deficiency. Various lipid emulsions are available, are commonly prescribed, and have been used for decades. Individual patients with bowel failure have been maintained on nutrition support for many, many years with weekly lipid infusions. These lipid emulsions tend to be well tolerated with adverse events noted in section 15.0.

1.5 Special Safety Considerations

We do not know whether lipids would influence the efficacy of chemotherapy. Two points suggest that lipids would not do so. First, prior studies with Doxil® and carboplatin show that these drugs together have favorable antineoplastic activity; analogously, a lipid emulsion **would not appear to detract** from the antineoplastic effects of either of these platinum-based agents [22-30]. Second, parenteral nutrition that includes concomitant lipid administration to increase caloric content is used often in various cancer settings, such as in patients undergoing bone marrow transplantation and in perioperative patients with severe malnutrition.

However, in an effort to be extra cautious in the current study, we will monitor patients closely during the trial, and we will also exclude patients who are being treated with curative intent.

1.6 Pathobiology.

Because of the life-threatening nature of carboplatin and oxaliplatin reactions, pragmatic considerations have resulted in sparse studies on pathobiology. These studies indicate these reactions are commonly type I and less commonly type IV [31,48]. First, emphasizing their type I nature, Iwamoto and others observed CD203c, a basophil surface marker of IgE-mediated type I hypersensitivity reactions, was 15% higher in patients who had sustained a carboplatin-induced reaction compared to those who had not [48]. Second, Caiado and others reported that 59% of patients who had sustained a carboplatin reaction had a carboplatin-specific IgE [32]. Third, Hesterberg and others demonstrated serum tryptase elevation in patients with a carboplatin hypersensitivity reaction [10]. **Serum tryptase, the most abundant mediator of hypersensitivity reactions stored in mast cells,** is one of 4 key mediators that comprise a standard panel of diagnostic evidence of allergic reactions: 1) serum tryptase, 2) urine 11-beta prostaglandin F2 alpha (PGF2a), 4) urine leukotriene 4, and 5) urine N-methylhistamine, the latter three of which stem from the release of prostaglandins, leukotrienes, and histamine, respectively. This finding of tryptase elevation with carboplatin or oxaliplatin reactions further emphasizes that these are type I hypersensitivity reactions and suggests a role for this 4-mediator panel [48-52]. Fourth, workers exposed to platinum salts show reactions to metals are mast cell/basophil IgE-mediated [53-55]. Finally, and of special relevance, preclinical work indicates that, although carboplatin induces histamine release from mast cells, this agent does so by **unique, inexplicable mechanisms unresponsive**

to more conventional suppressive agents; therefore, **novel interventions** are needed to prevent these reactions [48]. These findings indicate that IgE-mediation plays a complex but not fully elucidated role in carboplatin and oxaliplatin hypersensitivity reactions. Thus, it is reasonable to use a standard panel of 4 mediators -- serum tryptase; urine 11-beta prostaglandin F2 alpha (PGF2a); urine leukotriene E4; and urine N-methylhistamine, the latter 3 of which have not been assessed in carboplatin or oxaliplatin reactions but logically stem from release of prostaglandins, leukotrienes, and histamine, respectively -- to understand pathobiology and its relevance [56].

1.7 Preliminary Data

At the Mayo Clinic in Rochester, Minnesota, 30+ unique patients underwent carboplatin desensitization over 1 year, with cumulative, multi-cycle patient costs of **$1 million – over 10-fold greater** than that incurred from routine outpatient carboplatin administration; these cost data further define the need for preventing hypersensitivity reactions. Although the number above **includes patients other than those with ovarian cancer**, maintaining a focus on one cancer type – specifically on patients with ovarian cancer – is of value, as it enables us to assess the clinical outcomes of a uniform patient cohort.

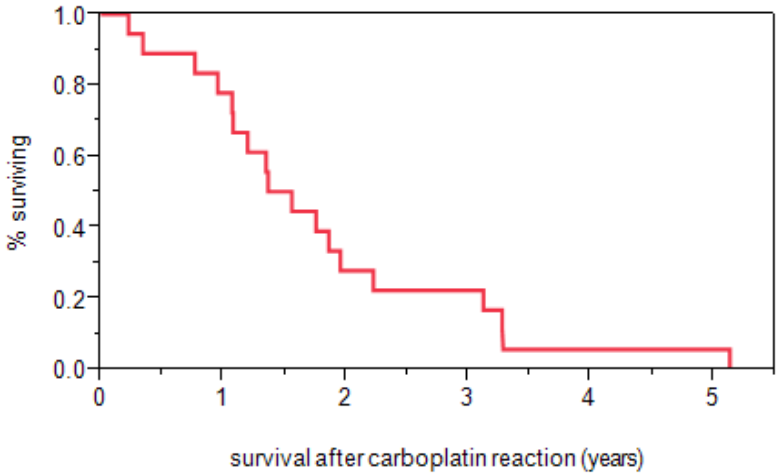


Figure 1: The median survival of ovarian patients who had a carboplatin reaction and who underwent desensitization was 1.4 years (95% confidence intervals: 1.07, 1.96 years). These data show that desensitization procedures are associated with long survival. These data suggest that the continued use of carboplatin and the investigation of approaches to reduce the risk of hypersensitivity reactions are justified.

Specific to ovarian cancer patients, our group reviewed recent outcome data from 18 consecutive ovarian cancer patients who underwent a carboplatin desensitization procedure. This cohort yields three observations that guide our proposed study design: 1) Patients developed a carboplatin reaction with the 8th (median) carboplatin treatment (range: 3, 21), thus providing justification for enrolling patients immediately before the 7th carboplatin treatment and, thus, in conjunction with data from other investigators, enabling us to estimate a realistic hazard ratio for our sample size calculations. Other investigators have similarly found that the risk of a hypersensitivity reaction increases markedly after 7 chemotherapy treatments. 2) Although half this cohort is deceased, the median survival of patients who sustained a carboplatin reaction and then underwent desensitization was 1.4 years (time from having sustained a hypersensitivity reaction to death or last follow up) with some patients living substantially longer (**Figure 1**). These observations further underscore the fact that carboplatin is a **key drug** in ovarian cancer and provides further motivation for investigating ways to administer this drug safely. 3) Two of these 18 patients developed **repeated reactions during their desensitization**. One required a **20-hour hospitalization for desensitization every time she received carboplatin**; this patient continued to react to the latter and needed to have her infusion

slowed. This observation **illustrates the need to prevent carboplatin reactions in the first place and the need to find ways to circumvent desensitization procedures.**

1.8 Summary

In view of the fact that reactions to carboplatin and oxaliplatin can compromise cancer care and can augment cost related to cancer care, we propose to test a simple, rationale, cost-effective prophylactic intervention, namely, the administration of lipids prior to patients' receiving their 7th or later infusion of either carboplatin or oxaliplatin. This proposal aims to test the hypothesis that lipids decrease the incidence of hypersensitivity reactions to these drugs within the context of a placebo-controlled trial.

1.9 Correlative Studies: Blood and Urine Markers

Although exploratory in nature, this aim would potentially afford the scientific underpinnings for a large scale clinical trial to be conducted in the Alliance for Clinical Trials in Oncology. This aim therefore plays an essential role in this pilot project. Laboratory endpoints will be checked only with the first dose of carboplatin following trial enrollment at three time points: within 24 hours prior to the lipid/placebo infusion (#1); after the lipids/placebo infusion (#2); and after the carboplatin/oxaliplatin infusion (#3) (**Figure 3**). Time point #2 will include only a blood check because of time constraints. Time points #1 and #2 are scientifically justified because all patients **will have received carboplatin/oxaliplatin earlier and are therefore potentially immunologically "primed"** to react to it. From a practical standpoint, it is **unlikely** that a patient who has sustained the trauma of a reaction would be willing to have her blood/urine checked at time point #3; nonetheless, time points #1 and #2 enable us to learn whether lipids appear to modulate well-established mediators of hypersensitivity reactions and whether these established mediators/ biomarkers are able to predict reactions.

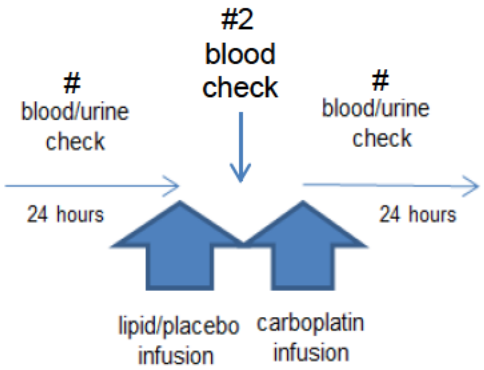


Figure 3: Translational endpoints will be assessed per the schema above at time points #1, #2, and #3.

We anticipate reporting data only descriptively (no sample size calculations) because of a high likelihood of patient drop-out at time point #3. Again, the purpose of this exploratory translational aim is to acquire **preliminary evidence of the immunomodulatory effects of lipids on mediators of hypersensitivity reactions.**

Assays. We will focus on four mediators, all with inter- and intra-test coefficients of variation of <15% (**Figure 4**). Blood and urine will be obtained, per the three time points in **Figure 3** where carboplatin refers to either carboplatin or oxaliplatin, with the first cycle of carboplatin following enrollment. We choose to focus on only the first cycle because 1) this allows us to accomplish our goal of acquiring evidence of the immunomodulatory effects of lipids

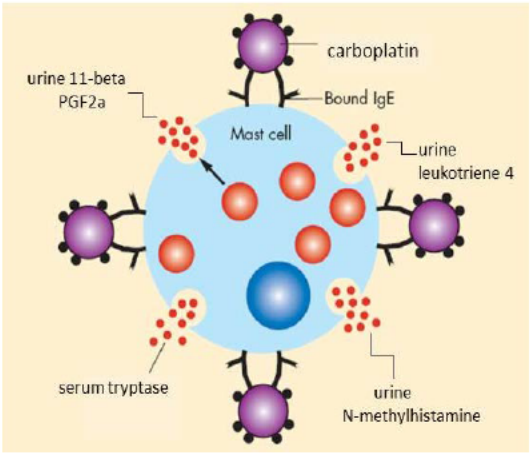


Figure 4: Four well-established mediators of hypersensitivity reactions -- serum tryptase, urine 11-beta prostaglandin F2 alpha (PGF2a), urine leukotriene 4, and urine N-methylhistamine -- will be used as markers provide further clinical evidence of reduced hypersensitivity reactions with lipids adapted from Bax, et al, 2012).

as relevant to hypersensitivity reactions; 2) more frequent testing poses an undue patient burden; and 3) cost is otherwise prohibitive in this pilot trial setting.

2.0 Goals

2.1 To determine if the infusion of a lipid emulsion before each dose of chemotherapy appears to prevent carboplatin and oxaliplatin hypersensitivity reactions in high-risk patients.

2.2 To explore if lipid infusions modulate a well-established panel of mediators of hypersensitivity reactions and if these mediators appear to predict reactions.

3.0 Patient Eligibility

3.1 Inclusion criteria

3.11 Age ≥18 years

3.12 Advanced, incurable cancer

3.13 7th or later cycle of intravenous carboplatin or oxaliplatin infusion planned or 4 months after the first cycle of agent (whichever is of longer duration) ≤30 days after registration

3.14 Anticipated 2 or more subsequent chemotherapy infusions of either carboplatin or oxaliplatin at the time of study registration.
NOTE: The dose of carboplatin or oxaliplatin, choice of other chemotherapy, and other ancillary treatment, such as antiemetics, will be left to the discretion of the treating healthcare provider.

3.15 Willing to provide mandatory blood and urine specimens for correlative research.
Note: Can be waived with permission of Study Chair (documentation such as an email must be provided).

3.16 The following laboratory values obtained ≤30 days prior to registration:

- Serum creatinine ≤1.5 times the institutional upper limit of normal (ULN)
  Note: Can be waived with permission of Study Chair (documentation such as an email must be provided).
- Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) <3x the upper limit of normal.
- Triglycerides <500 mg/dL
- Alkaline phosphatase ≤3x the institutional upper limit of normal.

3.2 Exclusion Criteria

3.21 Concurrent liposomal doxorubicin or any other liposomal agent.

3.22 Prior carboplatin or oxaliplatin hypersensitivity reaction.

3.23 Taking aspirin, nonsteroidal anti-inflammatory agents, or zileuton ≤7 days prior to registration.
Note: Can be waived with permission of Study Chair (documentation such as an email must be provided).

3.24 Allergy to egg or egg byproducts.

4.0 Test Schedule

4.1 Study Calendar

Tests and procedures	≤30 days prior to registration	With the first on-study infusion of carboplatin or oxaliplatin	Immediately before each infusion of carboplatin or oxaliplatin	End of each cycle of carboplatin or oxaliplatin
History and exam including weight	X			X[1]
Serum creatinine	X			
AST or ALT	X*			
Triglycerides	X			
Alkaline phosphatase	X*			
Lipid/placebo infusion			X	
AE Assessment	X			X
Blood and urine collection for research purposes[R]		X		

*Should be retested every 3 months or per the discretion of the treating oncologist.

Maximum Cycle Length = 28 days (will vary by regimen)

Footnotes:
1. Weight only

R Research funded

4.2 Event Monitoring/Survival Follow-up

Once patient is no longer on treatment for this study, no further follow-up is required.

5.0 Stratification Factors

5.1 Chemotherapy agent: carboplatin versus oxaliplatin

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Correlative Research

6.121 A mandatory correlative research component is part of this study, but it can be waived with prior permission from the study principal investigator.

6.122 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.2 IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Verification

Prior to accepting the registration, registration application will verify the following:

- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Treatment location requirements

Treatment on this protocol must commence at Mayo Clinic Rochester under the supervision of a medical oncologist, pain specialist, or associated allied health personnel.

6.5 Start of treatment

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.6 Randomization and Blinding Procedures

6.61 The factors defined in Section 5.0 will be used as stratification factors.

6.62 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

- Chemotherapy agent: carboplatin versus oxaliplatin

6.63 The Registration Office will notify the Pharmacy of the assigned arm.

6.64 Blinding will be ensured by means of masking the infusion bag and the associated tubing. Only the pharmacy staff will know if a specific patient is receiving lipids versus saline.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent/Placebo	Dose	Route	Days[123]	Retreatment
Intralipid®	100 mL	IV	immediately prior to each dose of either carboplatin or oxaliplatin until the patient demonstrates a healthcare provider-witnessed hypersensitivity reaction	continue with each dose of chemotherapy
Placebo	100 mL	IV	immediately prior to each dose of either carboplatin or oxaliplatin until the patient demonstrates a healthcare provider-witnessed hypersensitivity reaction	continue with each dose of chemotherapy

1 Maximum Cycle Length will be 28 days. Cycle length will vary depending on the cycle of the chemotherapy regimen.
2. For all other chemotherapy agents, administer premeds, chemotherapy, lipid infusion, and then Carboplatin or Oxaliplatin.
3. Initiate infusions at 30 mL/hour (0.5 mL/minute) for 15 minutes; if no untoward effects occur, the infusion rate may be increased to 60 mL/hour (1 mL/minute) for 92.5 minutes. Subsequent infusions may be administered over 1 hour.

7.2 Blood and Urine Markers

See Section 14.0

7.3 Breaking Codes in Double–Blinded Studies

Situations requiring codes to be broken: There are three distinct situations in which it is appropriate to break the codes for individual patients enrolled in double-blind trials:

(1) In the event of an emergency for an individual patient.

(2) In the event that it would be helpful for the future clinical care of an individual patient after she/he has completed participation in the trial.

In the event of an emergency, call the MCCC Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the MCCC Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that MCCC Registration Office personnel can return the call the next business day.

If, in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the MCCC Registration Office may be called [redacted] to find out which study therapy the patient was receiving.

8.0 Dosage Modification Based on Adverse Events

If a patient develops unexpected toxicity (≥CTCAE Grade 3) attributable to the lipid infusion from the lipids/placebo, this treatment should be stopped. The patient should then go off study.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should otherwise receive full and appropriate supportive care as clinically indicated.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

[redacted]

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 **Expedited Reporting Requirements for Commercial or Commercial Imaging Agents (Non-IND/IDE) Agent(s) ONLY:**

10.41 Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour 3 Calendar Days

Not resulting in Hospitalization ≥24 hrs	Not required	7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form [redacted] to submit to [redacted] The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or

progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal

conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Immune system disorders	Allergic reaction	X	X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Alkaline phosphatase	X	X
	Weight gain		X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Measurement of Effect

Measurement of effect will be determined based on whether a patient developed a healthcare provider-witnessed hypersensitivity reaction or not per CTCAE v 4.03

Patients who stop carboplatin or oxaliplatin for any reason other than a hypersensitivity reaction will be censored on the date of their last study infusion.

12.0 Descriptive Factors

12.1 Cancer type: ovarian cancer vs endometrial cancer vs colon cancer vs other cancer

12.2 Has the patient had an interval of 12 months or longer at any time between carboplatin/oxaliplatin treatments? yes versus no

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received treatment, on-study material must be submitted.

13.2 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted.

13.3 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. If the patient never received treatment, on-study material must be submitted.

13.4 Off study

Patients will go off study for the following reasons:

- Investigator discretion
- Treatment related adverse event (immune reaction or unexpected CTCAE ≥Grade 3 event)
- Switching to different chemotherapy
- Refusal of further treatment on this study
- Death

Patients will go off study and no further follow-up is required.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol*

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	24 hours prior to lipid/placebo infusion	Within 2 hours following lipid infusion	24 hours after chemo infusion	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Blood [1] (Section 14.4)	Mandatory	Whole Blood	Red top	10 mL	X	X	X	Yes	-80 degrees Centigrade
Urine[2] (Section 14.4)	Mandatory	24 hour urine		10 mL	X		X	Yes	-80 degrees Centigrade

1. Blood draw timed with dropping off of the 24 hour urine collection.
2. The patient may pick up kit prior to starting the infusion but must wait to start collection until infusion has been completed.

14.2 Collection and Processing

14.21 Blood samples will be centrifuged. Serum will be removed and stored at -80 degrees Centigrade for assay completion at a later date.

14.22 24 hour urine samples will be have a small aliquot of 10 cc removed, frozen at -80 degrees Centigrade and stored for assay completion at a later date.

14.3 Shipping and Handling

14.31 Kits will not be used.

14.32 After collection, blood and urine will be stored for future assays as noted below.

14.4 Background and Methodology

14.41 Serum tryptase will be measured with a quantitative enzyme-linked immunosorbent assay [59-61]. Based on previous data from our group, we anticipate a level of 11 ng/mL or greater at time point #1 in patients at risk for a hypersensitivity reaction (we hypothesize we will subsequently observe this reaction in the placebo group, although we will be agnostic to biomarker results at the time of carboplatin infusion) with a drop to below this level with lipids and no change with placebo at time point #2, and with a sustained drop with lipids and no change with placebo at time point #3 [59-61].

14.42 11-beta PGF2a, the most abundant prostaglandin D2 metabolite, will be assessed with a 24 hour urine collection with an immunoassay kit at time points #1 and #3. We anticipate a level of >1000 ng/24 hours or greater in patients about to sustain a carboplatin reaction at time point #1 (we hypothesize we will subsequently observe this reaction in the placebo group, although we will be agnostic to real time biomarker results during the carboplatin infusion) with a drop to below this level with lipids and no change with placebo at time point #3 [59-61].

14.43 Leukotriene E4 will be measured in urine with liquid chromatography-tandem mass spectrometry. We anticipate a concentration of >104 pg/mg or greater at time at time point #1 in patients about to sustain a carboplatin reaction (we hypothesize we will subsequently observe this reaction in the placebo group, although we will again be agnostic to real time biomarker results) with a drop with lipids and no change with placebo at time point #3 [59-61].

14.44 N-methylhistamine will be also assessed in urine. We anticipate a level of >200 mcg/g or greater at time point #1 in patients about to sustain a carboplatin reaction (we hypothesize we will subsequently observe this reaction in the placebo group, although we will again be agnostic to biomarker results) with a drop with lipids and no change with placebo at time point #3 [59-61].

15.0 Drug Information

15.1 Intravenous Fat Emulsion 20% (Intralipid® 20%)

15.11 Background:
Intravenous Fat Emulsion 20% is a sterile, non‑pyrogenic fat emulsion prepared for intravenous administration as a source of calories and essential fatty acids. We will purchase this product and will test it because 1) most published reports on the resuscitative role of lipids for drug overdoses used the same or similar formulations and 2) a safety record is well-established.

15.12 **Formulation**:
The lipid emulsion used in this study will consist of 100 mL of Intralipid® 20%, which contains 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. The major fatty acid components include linoleic acid (44-62%), oleic (19-30%), palmitic (7-14%), linolenic (4-11%), and stearic (1.405.5%). Intralipid 20% is available in 100 mL, 250 mL, and 500 mL fill sizes. The Intralipid 20% utilized in this study will be supplied in a 100 mL bags.

15.13 **Preparation and storage**:

Administer by IV infusion only via a separate peripheral line. Use a Baxter 1.2 micron in-line filter set (set #2H8486) which is a non-DEHP administration set. **Note: Filters of less than 1.2 micron pore size must not be used. Also, conventional administration sets contain polyvinyl chloride (PVC) components that have DEHP (di(2- ethylhexyl) phthalate) as a plasticizer. Fat‑containing fluids such as Intralipid® 20% extract DEHP from these PVC components.**

Pharmacy will mask the infusion by placing an amber bag over the IV bag and set.

Intralipid® 20% should not be stored above 25°C (77°F). Do not freeze Intralipid® 20%. If accidentally frozen, discard the bag. admixture instructions, light sensitivity, temperature for storage, product specific information.

15.14 **Administration:**
Initiate infusions of 20% emulsions at 0.5 mL/minute for 15 to 30 minutes; if no untoward effects occur, the infusion rate may be increased to 1 mL/minute.

15.15 **Pharmacokinetic information**:
Metabolism: Fatty acids, phospholipids, and glycerol are metabolized by cells to adenosine triphosphate (ATP), carbon dioxide, and water

Half-life elimination: 0.5 to 1 hour

Excretion: Biliary (phospholipids)

15.16 **Potential Drug Interactions**:
Premedications and chemotherapy agents may be incompatible with fat emulsions. Therefore, a separate peripheral site should be used to infuse the fat emulsion.

15.17 **Known potential toxicities**:

Adverse Reactions Significant 1% to 10%:
Endocrine & metabolic: Hyperglycemia, hyperlipidemia
Gastrointestinal: Nausea, vomiting
Hematologic & oncologic: Hypoproteinemia
Hepatic: Abnormal hepatic function tests

Frequency not defined:
Gastrointestinal: Gallbladder disease
Genitourinary: Urinary tract infection
Hepatic: Hepatic abnormality
Infection: Septicemia
Miscellaneous: Fever

<1% (Limited to important or life-threatening): Decreased INR, diarrhea, hypersensitivity reaction (including rash and dyspnea)

Consult the package insert for the most current and complete information.

15.18 **Drug procurement:** This product is manufactured by Fresenius Kapi, Uppsala, Sweden for Baxter Healthcare Corporation, Deerfield, IL.
Drug will be purchased through our usual pharmacy purchasing channels and received at the following shipping addresses:

Mayo Clinic Rochester
Attn: Cancer Center Research Pharmacist


15.19 **Nursing Guidelines:**

15.191 Fat emulsion 20% should be delivered via a separate peripheral IV infusion line, with a 1.2 micron in-line-filter set.

15.192 Infusion should start at 0.5 ml/minute if no problems after 15-30 minutes infusion may be increased to 1 ml/minute. Consult the protocol for specific administration rates.

15.193 Fat emulsion 20% can cause hyperglycemia and hyperlipidemia. Monitor labs as outlined in the protocol

16.0 Statistical Considerations and Methodology

16.1 Endpoints

16.11 Primary Endpoint:
The primary endpoint of this pilot study is **time-to-carboplatin or oxaliplatin acute hypersensitivity reaction** of any grade.

16.12 Translational Endpoint:
We will measure whether lipid infusions modulate a well-established panel of mediators of hypersensitivity reactions that appear to predict reactions.

16.2 Study Design

This is a prospective randomized study to explore whether the infusion of a lipid emulsion (versus placebo) prior to carboplatin or oxaliplatin in high risk patients leads to a decrease in incidence of hypersensitivity reactions . Patients will be randomized in a 1:1 ratio to receive a lipid emulsion versus placebo.

16.3 Analysis Plan

16.31 Primary endpoint: The primary endpoint is the time to healthcare provider reported hypersensitivity reactions from either carboplatin or oxaliplatin. Kaplan Meier curves will be constructed and a log-rank test will be used to compare time-to-hypersensitivity reaction between treatment arms. Data will be censored based on last infusion with no hypersensitivity reaction with a maximum study treatment duration of 2 years per patient.

16.32 Translational Endpoint: Mediators of hypersensitivity reactions will be assessed in an exploratory fashion to see if they appear to predict hypersensitivity reactions. Due to the nature of this pilot study, results will be summarized and tabulated. Graphics will be used as appropriate, and any testing will be hypothesis generating.

16.4 Sample size

Our target sample size is 40 patients (20/arm). If the true hazard ratio is 3.8 (with a median time to a reaction of approximately 2 months, based on our preliminary data and Table 1 data and based on our inclusion criterion that a patient must be starting the 7^{th} cycle of chemotherapy), 20 patients total (10/arm) provides 80% power to detect a prolongation of time-to-hypersensitivity reaction with lipids versus placebo with a 1-sided 5% significance level. Because patients will be censored upon stopping carboplatin or oxaliplatin for a reason other than a hypersensitivity reaction (per section 11.0), we conservatively anticipate high rates of censoring and therefore plan to accrue an extra 20 patients to reach our target sample size of 40 (20 per arm). A log-rank test will be used to compare time-to-carboplatin reactions between arms; a p-value of < 0.05 will be considered statistically significant.

16.5 Accrual and Duration of Study

We plan to accrue 40 patients (20 per arm) to this trial to ensure we have 20 (10/arm) evaluable patients. We estimate an accrual rate of 2 patients per month so that we expect

to complete accrual within 2 years. With an expected total time of treatment of 4 months, the expected total duration of the study is slightly over 2 years.

16.6 Missing Data

Missing data are expected to be low in this prospective study primarily because the occurrence of a hypersensitivity reaction will be well-documented in a real-time manner based on the medical necessity. Patients will not be replaced. Nonetheless, we will record and summarize the missing data and look for patterns. In the event, we were to identify patterns, we will decide on the appropriate strategies to account for missing data in our analyses plans. For now, we anticipate that we will rely heavily on censoring; we have inflated our sample size based on anticipated high rates of censoring.

16.7 Data and Safety Monitoring

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.8 Adverse Event Stopping Rules

Note: Carboplatin and oxaliplatin are not the study drugs of interest. All adverse event attributions should be made to the lipid/placebo infusion, not to carboplatin/oxaliplatin.

16.81 The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

16.82 Adverse events will be monitored separately by arm; the principal investigator will remain blinded. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- if there are 2 or more Grade 3 or higher adverse events at least possibly attributable to lipids in the first 5 patients on the lipid arm.
- if after the first 5 patients on the lipid arm have been treated, there are 40% or more patients with Grade 3 or higher adverse events at least possibly attributable to lipids.
- if any Grade 5 adverse events are observed that are related to study treatment (lipids/placebo).

Note: Historically, lipids have been administered frequently in cancer settings with minimal toxicity. We do not expect any further complications due to the lipids. With that in mind, we maintain a cautious mindset when monitoring these toxicities.

16.83 If accrual is temporarily suspended, the study will be reviewed to determine whether accrual should continue or be permanently closed.

16.84 We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.9 Gender and minority accrual considerations

This study is open to patients from all races. Historical data indicate that no more than 10% of patients will be ethnic minorities. Subset analysis along ethnic subpopulations will hence have a lack of power to draw substantive conclusions but will provide some data for future meta-analytic procedures and hypotheses generation.

	Sex/Gender (%)			
Ethnic Category	**Females**	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	25	14	0	39
Ethnic Category: Total of all subjects	25	15	0	40
Racial Category				
American Indian or Alaskan Native	1	0	0	1
Asian	2	1	0	3
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	1	0	1
White	21	12	0	33
Racial Category: Total of all subjects*	25	15	0	40

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens - Not applicable

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See Section 4.0 and Data Submission Schedule for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

As required by the protocol – documentation from a healthcare provider proving hypersensitivity reaction per Section 7.0

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the Data Manager will query the site. The query will be sent to the appropriate site to make the correction and return the query and documentation of correction back to the Data Manager.

19.0 Budget

19.1 Costs charged to patient

Routine clinical care

19.2 Tests that will be research funded

Research testing on blood and urine

19.3 Other considerations

Lipid emulsion and placebo will be provided by the study.

20.0 References

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